Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3, 5-8, 11 and 13-45 are pending in the application, with claim 1 being the sole independent claim. Claim 9 has been canceled without prejudice or disclaimer of the subject matter therein. Support for the amendment to claim 1 can be found in previous claim 9, in the claims as originally filed and in paragraphs [0008], [0022], [0097] and [0098] of the published application, this corresponds to paragraphs [0006], [0019], [0094] and [0095] of the as-filed specification. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Interview

Applicant thanks Examiner Hines and her Supervisor Examiner Foley for the courtesy of granting Applicant a personal interview conducted on March 5, 2008. All outstanding rejections were discussed.

During the interview, Applicants presented six exhibits. Specifically, Applicant provided a copy of Evans *et al.* "Characterization and Biological Evaluation of Microparticle Adjuvant Formulation for Plasmid DNA Vaccines," *J. Phamr. Sciences* 93:1924-1939, Wiley-Liss (2004), previously provided with the Reply of August 17, 2007. Applicants specifically directed the Examiner's attention to p. 1935, col. 1, ll. 20-

30, p. 1937, col. 1, ll. 28-31, and p. 1937, col. 1, l. 49 to col. 2, l. 1. Much of the data presented in this exhibit was already disclosed in the reference of Evans (WO 02/00844). Additionally, Applicant provided a copy of pages 45-47 and figures 11-13 of the previously cited Evans (WO 02/00844) reference, and a copy of pages 30-36 of the previously cited Musunuri *et al.* (WO 99/21591) reference. All other exhibits shown during the interview are now incorporated into the present Amendment and Reply.

During the interview, Examiner Foley indicated that the limitation "cold filtering" in claim 1 was unclear and suggested amending the claim to clarify this limitation. Upon further review of the specification, Applicant asserts that the limitation "cold filtering" is sufficiently defined in the specification. The specification provides that

> [t]he cold filtration step must take place at a temperature below the cloud point of the block copolymer comprised in the formulation. The cold filtration step is suitably performed at a temperature between about -2°C. to about 8°C. For example, the cold filtration step can be performed at about -2°C., at about -1°C., at about 0°C., at about 1°C., at about 2°C., at about 3°C., at about 4°C., at about 5°C., at about 6°C., at about 7°C. or at about 8°C.

(Paragraph [0097] of the published application, corresponding to paragraph [0094] of the as-filed specification, emphasis added.) As such, Applicant respectfully disagrees with the Examiner's position. However, solely in an effort to advance prosecution, and not in acquiesce to any reasoning underlying the Examiner's objection, Applicant has amended the claim to indicate that the cold filtration step takes place at a temperature below the cloud point of the block copolymer.

Rejections under 35 U.S.C. § 112

The Examiner had rejected claims 1-3, 5-9, 11 and 13-45 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement, this is a new matter rejection. Specifically, the Examiner asserts that "paragraph [008] is drawn to the combination of ingredients within the lyophilized composition, *i.e.*, the block copolymer, the polynucleotide molecules, a cationic surfactant and an amorphous cryoprotectant and bulking agent. There is no teaching of mixtures of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers and proteins." (OA at page 5.) Applicant respectfully traverses this rejection.

Proper descriptive support for the presently pending claims can be found in the originally filed claims as well as in the specification as-filed. The Examiner is reminded that descriptive support does not require an *ipsis verbis* description of the claimed subject matter. The standard for finding proper descriptive support as set out in the MPEP §2163 asks whether a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification. *See, e.g.*, *Vas-Cath*, 935 F.2d at 1563, *Martin v. Johnson*, 454 F.2d 746, at 751 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient"). Here, the original claims recited that the composition comprises at least one amorphous cryoprotectant or at least one crystalline bulking agent. (*See* originally filed claims 10 and 12.) Thus, the claims as originally filed included compositions comprising a combination of more than one amorphous cryoprotectant or more than one crystalline bulking agent. In addition, paragraph [0008] of the published application refers to

combinations of amorphous cryoprotectants and crystalline bulking agents. Specifically, paragraph [0008] reads as follows:

> In one aspect, the invention provides a method of preparing a lyophilized composition comprising mixing a block copolymer with a population of polynucleotide molecules, a cationic surfactant, **and an amorphous cryoprotectant or a bulking agent or any combination thereof**, at a temperature below the cloud point of the block copolymer to form a mixture. . . .

(Paragraph [0008] of published application, corresponding to paragraph [0006] in the as-filed specification, emphasis added.) Here, paragraph [0008] indicates that the "combination thereof" is directed to the combination of amorphous cryoprotectants and crystalline bulking agents. The specification provides several non-limiting examples of amorphous cryoprotectants and crystalline bulking agents.

Amorphous cryoprotectants	**Crystalline bulking agents**	Paragraph # in published application
Sugars	Sugars	[0011]
Sucrose (disaccharide)	Sucrose (disaccharide)	
Lactose (disaccharide)	Lactose (disaccharide)	
Trehalose (disaccharide)	Trehalose (disaccharide)	
Maltose (disaccharide)	Maltose (disaccharide)	
Glucose (monosaccharide)	Glucose (monosaccharide)	
Monosaccharides (fructose, galactose, glucose)		[0082]
Disaccharide (sucrose, lactose)		
Oligosaccharides		
Polyols (glycerol, sorbitol)		
Proteins (albumin)		
Hydrophilic polymers (polyethylene glycol)		
	D-manitol (sugar alcohol, polyol)	[0084]
	Trehalose (disaccharide)	
	Dextran (disaccharide)	

As seen in the table above, several compositions have dual functions; they can be both an amorphous cryoprotectant and crystalline bulking agent at the same time. (*See* paragraph [0083] of the published application.) The limitation "any combination thereof" is directed to combinations of amorphous cryoprotectants and crystalline bulking agents. These combinations can include more than one amorphous cryoprotectant or more than one crystalline bulking agent or a combination of a crystalline bulking agent and an amorphous cryoprotectant. Thus, Applicant asserts that the specification as filed provides proper descriptive support for mixtures of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers and proteins. However, solely in an effort to advance prosecution and not in acquiesce of any of the Examiners assertions, Applicant has amended claim 1 to recite any "combination thereof." Support for this amendment is found in paragraph [0008] of the published application. Applicant respectfully requests that the Examiner reconsider and withdraw the new matter rejection as it may apply to the presently pending claims.

Rejections under 35 U.S.C. § 103

Claims 1-2, 5-9, 11, 13, 15-32, 37-39 and 40-45

The Examiner has rejected claims 1-2, 5-9, 11, 13, 15-32, 37-39 and 40-45 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Evans (WO 02/00844) and Volkin *et al.* (WO97/40839; hereinafter "Volkin") further in view of Hunter *et al.* (U.S. Pat. No. 5,811,088; hereinafter "Hunter"). (OA at pages 6-12) The Examiner asserts that

> one of ordinary skill in the art would have had a reasonable expectation of success by modifying the method of preparation because both Evans and

> Volkin *et al.*, teach the desirability of providing formulations containing block copolymers at a temperature at which they are soluble, *i.e.*, below the cloud point, and Hunter *et al.* teach cold filtration of those same soluble block co-polymers in an ice-cold phosphate buffered saline since filtration of the mixture rather than separate filtration clearly saves time and materials.

(OA at page 11.) The Examiner further asserts that "no more than routine skill would have been required to incorporate the method and formulations as taught by Hunter *et al.*, in the method and formulation of Evans and Volkin *et al.*, since Hunter *et al.*, teach saving time and materials to sterilize the compositions after they have been mixed and rather than separately and individually threat the components." (OA at page 12.) Applicant respectfully traverses this rejection.

The references cited by the Examiner do not disclose all of the elements of the present claims. Thus, the Examiner has not satisfied the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). The factors to be considered under 35 U.S.C. § 103(a) are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and MPEP §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The critical role of the Office personnel as fact finders when resolving Graham inquiries has recently been emphasized by the Office within its published Examination Guidelines. *See* Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International v. Teleflex Inc.* Fed. Reg. 72:57526-57535 (October 10, 2007), hereinafter "Examination Guidelines." To establish a *prima*

facie case of obviousness it is not sufficient to merely combine individual elements known in the prior art if the results would not have been predictable to one of ordinary skill in the art (*see* Examination Guidelines at page 57529). Establishment of a *prima facie* case of obviousness requires that the Examiner factually show that the references in combination teach all of the elements of the claims, as well as provide a reasoned articulation that the combination of elements would have been known to produce a predictable result.

Evans discloses that mixtures of BAK and DNA forms precipitates in the presence of the copolymer at temperatures below the below the cloud point of the copolymer

Evans does not teach a method of producing a mixture comprising a cationic surfactant, a block copolymer, a polynucleotide, and a compound selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and any combination thereof, cold filtering the mixture followed by lyophilizing the mixture.

Evans teaches a mixture comprising DNA, BAK and a copolymer. Evans teaches that this mixture forms vesicles above the cloud point of the block copolymer and forms DNA/BAK precipitates when the temperature is reduced below the cloud point of the block copolymer (below 8°C). "These data indicate that the DNA/BAK precipitates in D118, formed at temperatures below the cloud point, were completely dissolved above the cloud point." (Evans, page 46, lines 18-20.) D118 is a mixture comprising 7.5 mg/ml CRL-1005, 0.45 mM BAK, and 5 mg/ml DNA. (*See* Evans page 49, table 7.) Evans discovery was that the usual DNA/BAK precipitates also form in a mixture of DNA/BAK/copolymer at a temperature below the cloud point of the copolymer, these

DNA/BAK precipitates disappear once the mixture is raised to ambient temperature, *i.e.*, above the cloud point of the block copolymer.

Evans recognizes that at the time the present invention was made it was known that compositions comprising mixtures of DNA/BAK form precipitates. Figure 11 depicts the formation of precipitates in a mixture of DNA/BAK. The experiments disclosed in Figure 11 are carried out at ambient temperature (25°C). (*See* Evans, pages 45-47, Example 10.) Here, DNA by itself does not form precipitates, and the combination of 7.5 mg/ml CRL-1005, 0.45 mM BAK, and 5 mg/ml DNA also does not form precipitates. In contrast, under the same conditions, the mixture comprising 0.45 mM BAK, and 5 mg/ml DNA does form precipitates at ambient temperature.

Evans teaches that the combination of DNA/BAK/copolymer at ambient temperature forms discrete vesicles with a defined narrow size range, while the DNA/BAK complexes very widely in size. Figure 12 depicts the particle size distribution in a composition comprising 5 mg/ml CRL-1005, 0.6 mM BAK, and 5 mg/ml DNA. The combination of DNA/BAK/copolymer results in a particle size raging from about 0.2 μm to 1 μm. (*See* Evans, Figure 11). While the combination of DNA/BAK forms particles ranging in size from 2 μm to greater than 1000 μm. Figure 13 shows another variation of the size distribution in copolymer containing particles versus particles comprising only DNA/BAK in phosphate buffered saline. In Figure 13, the size distribution of the DNA/BAK particles ranged from about 5 μm to approximately 50 μm.

Evans does not teach cold filtering of the mixture of DNA/BAK/copolymer to produce a sterile formulation. Furthermore, the ordinary artisan would know that

filtering a composition that comprises precipitates would tend to clog the filter, which can cause the filters to fail, and the resultant filtrate would not be guaranteed to be sterile. Here, the reference indicates that at temperatures below the cloud point of the block copolymer the DNA/BAK/copolymer mixture forms precipitates and above the cloud point of the block copolymer the mixture formes vesicles that are to large to pass through a filter sterilization assemble that has a pore size ranging from 0.5 to 0.25 μm.

Production of a sterile formulation comprising DNA and BAK requires the separate filtration of the individual components. (*See* Musunuri *et al.* p. 30, l 2 7 to p. 31, l. 1, and page 36, ll/ 3-4, 9-10 and 16-18.) All formulations in Evans were prepared by first mixing the pure copolymer with cold plasmid DNA, to this DNA/copolymer mixture BAK is then added to form a DNA/copolymer/BAK mixture. In a post filing date reference by Evans, sterile formulations of DNA/copolymer/BAK are made by first filtering the DNA/copolymer composition and the BAK composition separately before combining them to form a sterile mixture. (Exhibit A, previously submitted with the Amendment and Reply of August 17, 2007.) Thus, there is no indication in Evans that would lead the ordinary artisan to believe that mixtures of DNA and BAK can be filtered above or below the cloud point of the copolymer.

Volkin does not teach a mixture of DNA with a cationic surfactant or a mixture of DNA with a copolymer

Volkin teaches that DNA vaccine formulation containing sucrose and lactose greatly stabilize the DNA during lyophilized storage. Stability is measured by measuring the percentage of DNA that maintains the supercoiled structure as compared to the open circular or linear DNA structures, both structures are indicative of degraded DNA. Furthermore, the reference clearly indicates that while sucrose and lactose can stabilize

DNA "mannitol does not enhance DNA stability compared to solution control (in PBS)." (Volkin page 81, lines 11-14.) Volkin does not teach that the addition of an amorphous cryoprotectant helps stabilize the particle size and maintains population polydispersity that remains unchanged during the freeze-drying process. Volkin does not teach mixtures of DNA and a cationic surfactant, or DNA and a copolymer. Additionally, Volkin does not teach the use of cationic surfactant in combination with a block copolymer to stabilize the DNA formulation.

Hunter does not teach lyophilizing a copolymer, adding a cationic surfactant with a copolymer, adding a cryoprotectant or bulking agent with the copolymer, or adding DNA with the copolymer

Contrary to the Examiners' assertion, Hunter does not "teach saving time and material to sterilize the compositions after they have been mixed and rather than separately and individually treat the components." (OA at page 12.) The disclosure of Hunter does not cure the deficiencies of Evans and Volkin. Hunter does not teach filtering a mixture of DNA, a copolymer, a cationic surfactant, and a compound selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and any combination thereof. Example 4 in Hunter teaches the filtration of copolymers CRL-8131, CRL-8141, L103 and L023 after the copolymers were solubilized in ice cold phosphate buffered saline (PBS). The solubilized composition was then filter sterilized with a 0.22 μm filter. Here, the filtered composition consisted only of the copolymer and PBS without any other components. Furthermore, Hunter does not teach lyophilizing or freeze-drying the copolymer.

The combination of references does not lead to a predicable result because the references teach away from the present invention

The cited references teach away from sterile filtering a combination of cationic surfactant, DNA and copolymer mixtures. Evans teaches that the combination of BAK and DNA forms complexes or precipitates that are too large to filter. (*See* Evans, Example 10, Figures 11-13 and page 2, lines 27-28; citing Musunuri *et al.* WO 99/21591, cited by the Examiner in OA at page 18.) Specifically, the incorporated reference WO 99/21591 teaches complexing BAK and DNA for the purpose of formulating a composition that can be used to introduce DNA into a host or host cell. In order to prepare a sterile formulation that may be administered to an animal, the DNA and BAK stock solutions are filtered separately before the DNA and BAK are combined. (*See* WO 99/21591, Example 4.) WO 99/21591 teaches that once DNA and BAK are mixed, the mixture will either form a vesicular complex or a precipitate in aqueous solution. BAK alone does not form a vesicular structure or precipitate in aqueous solution and neither does DNA. Depending on the concentration of BAK in the BAK-DNA mixture, either a vesicular complex ranging in size from 50-400 nm will form or the mixture will form a snowy flocculent precipitate. (*See* WO 99/21591, Example 2.) Evans teaches that DNA/BAK in phosphate buffered saline will have a particle size distribution from about 1 μm to above 1000 μm. Thus, at the time the invention was made the ordinary artisan would have expected that a combination of cationic surfactant and DNA will result in the formation of vesicles and/or precipitates that cannot be filtered when combined together, and that the DNA and cationic surfactant would have to be filtered separately. The present invention is directed at filtering a mixture of DNA, a copolymer, a cationic surfactant, and a compound selected from the group consisting of

monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and any combination thereof, below the cloud point of the copolymer in a single cold filtration step.

Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531 (Fed. Cir. 1993). Evans teaches that DNA and BAK form precipitates in the presence of a copolymer while the solution is maintained below the cloud point of the copolymer. "These data indicate that the DNA/BAK precipitates in D118, formed at temperatures below the cloud point, were completely dissolved above the cloud point." (Evans, page 46, lines 18-20.) Evans does not make a sterile solution by filtering the combined mixture below the cloud point. "Preparation of sterile vaccine formulations requires only the addition of sterile BAK to a solution of DNA/CRL1005 that is sterile filtered below the cloud point." (*See* EXHIBIT A, previously submitted with the Amendment and Reply of August 17, 2007, page 1937, column 1, 3rd paragraph.) Thus, in the Evans post filing date reference the two stock components the DNA-CRL1005 mixture and the BAK solution are filtered separately before combing them to from a mixture. This is differs from the claimed invention which mixes all components and then uses only a single cold filtration step.

Unexpected results

Applicants have discovered that the process of making a sterile polynucleotide solution can be simplified by combining cationic surfactant/DNA/copolymer and a compound selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and any combination thereof,

below the cloud point of the copolymer and sterile filtering the mixture, packaging the mixture and storing the mixture. (*See* published application [0066].) Applicants have unexpectedly discovered that microparticle formation does not need to occur prior to sterilization and storage in the lyophilized form. (*See* published application [0066].) Contrary to the Examiner's assertion the ordinary artisan would not have been motivated to combine the teachings of Evans and Volkin in view of Hunter to arrive at the instantly claimed method of producing a sterile formulation of cationic surfactant, polynucleotide, copolymer, and a compound selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and any combination thereof. The ordinary artisan at the time the invention was made did not appreciate that a combination of DNA-BAK in the presence of a copolymer and an amorphous cryoprotectant does not form the expected BAK-DNA precipitate. Because DNA/BAK in the presence of a copolymer below the cloud point of the copolymer forms precipitates the ordinary artisan could not predict that the addition of a cryoprotectant or bulking agent to the mixture prevents the precipitation of the DNA and allows for the single step filtration of the mixture. As such, Applicant respectfully asserts that a *prima facie* case of obviousness has not been established and respectfully requests that the Examiner reconsider and withdraw the rejection.

Claim 3

The Examiner has rejected claim 3 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Evans (WO 02/00844), Volkin (WO97/40839) and Hunter (U.S. Pat. No. 5,811,088) further in view of Balasubramanian (U.S. Pat. No. 5,824,322). (OA at

pages 14-16) The Examiner asserts that "Balasubramanian teach the desirability of providing preparations containing physiologic phosphate buffered saline and freeze-dried (lyophilized) formulations." (OA at page 16.) Applicant respectfully traverses this rejection.

For the same reasons elaborated above, which are reiterated and entirely incorporated herein by reference, Evans, Volkin and Hunter would not have rendered the claims obvious under 35 U.S.C. § 103. Balasubramanian does not rectify the deficiencies of Evans, Volkin and Hunter. In order to properly combine references there must be "some articulated reasoning with some rational underpinning to support a legal conclusion of obviousness." *See KSR International Co v. Teleflex Inc.* , 127 S.Ct. 1727, at 1741 (2007), citing *In re Kahn,* 441 F.3D, 977, 988 (C.A.Fed. 2006.) Balasubramanian teaches the use of reverse tri-block copolymers with various immunogens. (*See* columns 17 and 18.) However, Balasubramanian is silent with regards to formulating the reverse tri-block copolymer with a polynucleotide, let alone in combination with a cationic surfactant. In addition, Balasubramanian is silent with regards to cold filtering a reverse tri-block copolymer/cationic surfactant/DNA composition. Additionally, there are no suggestion in Balasubramanian to sterile filter the mixture before lyophilizing the mixture. Applicant asserts that the Examiner has failed to establish a *prima facie* case of obviousness in combining the references because the Examiner has failed to articulate a rational that establishes the combination to lead to a predictable result. As such, Applicants respectfully requested reconsideration and withdrawal of the rejection.

Claims 11 and 13-14

The Examiner has rejected claims 11 and 13-14 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Evans (WO 02/00844), Volkin (WO97/40839) and Hunter *et al.* (U.S. Pat. No. 5,811,088) further in view of Musunuri *et al.* (WO 99/21591; hereinafter "Musunuri"). (OA at pages 18-20) The Examiner asserts that it would have been *prima facie* obvious at the time of applicants' invention to include concentrations of sucrose at about 10%v/v as taught by Musunuri *et al.*" (OA at page 19.) Applicant respectfully traverses this rejection.

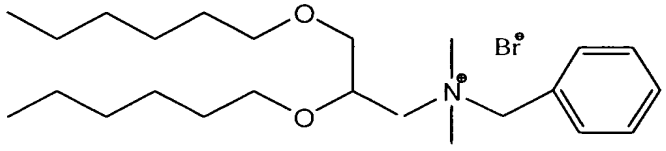
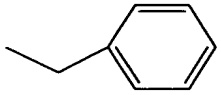
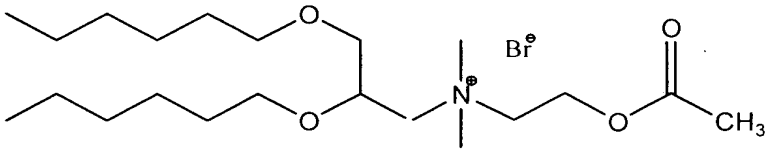
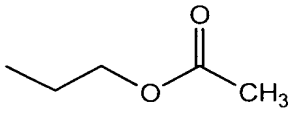
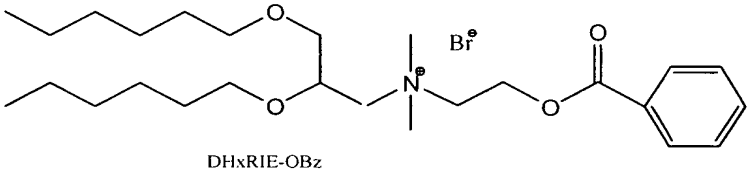
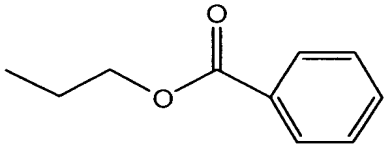
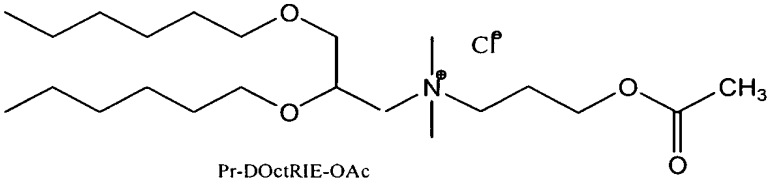
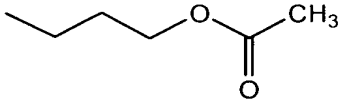
For the same reasons elaborated above, which are reiterated and entirely incorporated herein by reference, Evans, Volkin and Hunter would not have rendered the claims obvious under 35 U.S.C. § 103. Musunuri does not rectify the deficiencies of Evans, Volkin and Hunter. Musunuri does not teach mixing a polynucleotide, a cationic surfactant and sucrose mixture with a co-polymer followed by cold filtering the mixture before lyophilizing the composition. Musunuri teaches that DNA and BAK mixtures will form snowy flocculant precipitates at BAK concentration above 0.04% w/v BAK. (*See* page 33, lines 5-8.) This precipitate is undesirable and does not induce as strong of a humoral immune response. (*See* page 38, lines 17-28; and Figure 1.) Additionally, the reference teaches that the combination of BAK and DNA forms vesicular complexes similar to classical liposomes and cationic liposomes that can achieve particle sizes ranging from 50 nm to 230 nm in size. (*See* page 32, lines 16-26.) "Before admixture, both solutions are preferably filtered conventionally for example, using a 0.22 μm Millex GV syringe filter." (*See* sentence spanning page 30-31.) The ordinary artisan reading Musunuri would not be motivated to filter a composition comprising BAK and DNA,

because the mixture will form complexes having a diameter of 230 nm (0.23 μm), these complexes are large enough to clog a conventional filter assembly. Thus, the ordinary artisan reading Musunuri would not consider that filtering a mixture of DNA and BAK would a viable option to ensure sterility of the composition because it forms precipitates and vesicular structures. Furthermore, the reference is clear that it filters the stock components separately before mixing them. Applicants respectfully assert that this combination of references is insufficient to establish a *prima facie* case of obviousness. As such, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Claims 33-36

The Examiner has rejected claims 11 and 13-14 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Evans (WO 02/00844), Volkin (WO97/40839) and Hunter (U.S. Pat. No. 5,811,088) further in view of Felgner *et al.* (U.S. Pat. No. 5,459,127; hereinafter "Felgner"). (OA at pages 18-20) Specifically, the Examiner asserts that "Flegner *et al.* teach examples of useful cationic lipids to include (±)-N-(Benzyl)-N,N-dimethyl-2,3-bis(hexyloxy)-1-propanaminium bromide (Bn-DHxRIE), (±)-N-(2-Acetoxyethyl)-N,N-dimethyl-2,3-bis(hexyloxy)-1-propanaminium bromide (DHxRIE-OAc), (±)-N-(2-Benzoyloxyethyl)-N-,N-dimethyl-2,3-bis(hexyloxy)-1-propanaminium bromide (DHxRIE-OBz) and (±)-N-(3-Acetoxypropyl)-N,N-dimethyl-2,3-bis(octyloxy)-1-propanaminium chloride (Pr-DOctRIE-OAc)." Applicants respectfully traverse this rejection.

For the same reasons elaborated above, which are reiterated and entirely incorporated herein by reference, Evans, Volkin and Hunter would not have rendered the claims obvious under 35 U.S.C. § 103. Felgner does not remedy the deficiencies of Evans, Volkin and Hunter. Contrary to the Examiners assertion, the Felgner reference does not teach or disclose cationic surfactants having the following polar head groups:

Structures of the presently claimed cationic surfactants	Polar Head groups **not taught** by Felgner
 Bn-DHRIE	
 DHxRIE-OAc	
 DHxRIE-OBz	
 Pr-DOctRIE-OAc	

The Felgner reference does not teach or suggest the specifically recited compounds: Bn-DHxRIE, DHxRIE-OAc, DHxRIE-OBz and Pr-DOctRIE-OAc. Thus, the combination of references is missing the element of the specific cationic surfactant of selected from

the group consisting of Bn-DHxRIE, DHxRIE-OAc, DHxRIE-OBz and Pr-DOctRIE-OAc. Because the combination of references has not taught all the recited elements, Applicant asserts that the Examiner has not met their burden of establishing a *prima facie* case of obviousness based on the cited references. As such, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Conclusion

Applicants invention comprises, for example, mixing the following components at a temperature below 8°C:

- DNA
- BAK
- Copolymer
- Sucrose

Surprisingly, NO precipitate forms in this mixture below the cloud point of the copolymer, and this allows the solution to be cold filtered at a temperature below 8°C.

In contrast, the cited references fail to establish a *prima facie* case of obviousness based on the references as a whole. The teachings of the cited references are summarized in the table below.

	Evans	**Volkin**	**Hunter**	**Musunuri**
25°C	DNA BAK Copolymer NO Precipitate	DNA Sucrose Salt NO Precipitate		DNA BAK Sucrose **PRECIPITATE**
Below 8°C	DNA BAK Copolymer **PRECIPITATE**		 Copolymer NO Precipitate Filter sterilize	
Storage	frozen	lyophilize		

There is nothing in the references as a whole that would lead the ordinary artisan to predictably conclude that adding sucrose to a DNA, cationic surfactant and copolymer mixture below the cloud point of the copolymer would lead to a mixture that does not form precipitates. Especially considering that it was known that a mixture of DNA,

cationic surfactant and sucrose at ambient temperature either forms complexes or precipitates neither of which can be sterile filleted.

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Ulrike Winkler Jenks
Attorney for Applicant
Registration No. 59,044

Date: 3/10/08

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
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